The relationship between sleep problems and autism spectrum disorders among preschool children with anxiety disorders

A causal mediation analysis

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Abstract

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Title:	The relationship between sleep problems and autism spectrum disorders among preschool children with anxiety disorders
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Background: Anxiety symptoms are among the most commonly observed and impairing symptoms associated with autism spectrum disorders (ASD). In addition, parents of children with ASD frequently report that their children have sleep disturbances. The current study´s main hypothesis is that there is a significant relationship between ASD and anxiety in preschool children within the autism spectrum. Secondly, it is hypothesized that this relationship between ASD and anxiety are mediated by sleep problems. The anxiety-subtypes examined were generalized anxiety, separation anxiety, social anxiety and specific anxiety.

Method: The data used in the current study are part of the Autism Birth Cohort Study (ABC-Study), a case cohort study nested within the population-based Norwegian Mother and Child Cohort Study (MoBa), at the Norwegian Institute of Public Health. To test the hypotheses, bivariate logistic regression analysis was used in accordance to the principles of causal mediation analysis. The student participated in the clinical assessment at the ABC-clinic.

Results: A significant relationship between ASD and generalized anxiety was found. In addition, there was a significant association between ASD and sleep problems at 18 months of age. The association was even stronger at 36 months of age. A significant association between sleep problems at 18 months and generalized anxiety in preschool children was found, even if we adjusted for anxiety at 18 months. The effect of ASD on generalized anxiety was reduced when we adjusted for sleep problems at 18 months. This may suggest that sleep problems at 18 months have at least a partially mediating effect on the relationship between ASD and generalized anxiety. No relationship was found between ASD and the remaining subtypes of anxiety, separation anxiety, specific anxiety and social anxiety, in this sample.

Conclusion: The significant relationship between ASD and generalized anxiety can at least partially be accounted for by the mediating role of sleep problems in children with ASD.

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1 Introduction

The relationship between autism spectrum disorders (ASD) and anxiety has been a central topic in recent years. A review conducted in 2009 showed that it is evident that anxiety is a significant problem for a substantial proportion of children with ASD (White, Oswald, Ollendick, & Scahill, 2009).

In addition to this research, it has been increasing interest in the importance of sleep in the first years of life, both in the general population (Gregory & O´Connor, 2002) and among children with ASD (Krakowiak, Goodlin-Jones, Hertz-Picciotto, Croen, & Hansen, 2008). Sleep is argued to be fundamental for emotional development in infants and children (Gregory & O´Connor, 2002). Regarding children with ASD, it has been found that these children are likely to have more disturbed sleep than typically developing children, as well as those with other developmental disabilities (Humphreys, Gringras, Blair, Scott, Henderson, Fleming, & Emond, 2014). To date, no research has been conducted on the relationship between sleep problems and ASD in preschool children with anxiety disorders. This is an important area to study because of the potential mediating effect of sleep problems on development of psychopathology.

White and Roberson-Nay (2009) argue that research is needed to identify risk factors and etiological pathways for anxiety in ASD. In particular, prospective longitudinal studies are necessary to clarify the relationship between sleep problems and subtypes of anxiety (Alvaro, Roberts, & Harris, 2014).

To meet these needs, the current study aims to assess the role of early-age -sleep problems in preschool children with ASD and anxiety, using prospective longitudinal data. The current study´s main hypothesis is that there is a significant relationship between ASD and anxiety. Secondly, it is hypothesized that the relationship between ASD and anxiety, at least partially, is mediated by sleep problems. To the best of our knowledge, this has not previously been examined.

1.1 Autism spectrum disorders

1.1.1 History

Leo Kanner, a psychiatrist at Johns Hopkins University, first described autism, in 1943, in a small group of children who demonstrated extreme aloofness and total indifference to other people (Johnson & Myers, 2007; Kanner, 1943). Kanner´s case-stories shared unique and previously unreported patterns of behavior including social remoteness, obsessiveness, stereotypy and echolalia (Engeland & Buitelaar, 2008). Echolalia is defined as an automatic repetition of vocalizations made by another person (McEvoy, Loveland, & Landry, 1988). Unaware of Kanner´s work, Hans Asperger, an Austrian pediatrician, published an article in 1944 that described children who demonstrated symptoms similar to those of Kanner's patients, with the exception that verbal and cognitive skills were higher (Johnson & Myers, 2007). Over the past decades, clinical and research interest has focused on the heterogeneity of these conditions (Johnson & Myers, 2007). The term autism spectrum disorder (ASD) is presented in the following section describing the clinical features which individuals with ASD share and those features that differ.

1.1.2 Clinical features of ASD

ASDs constitutes a heterogeneous group of neurodevelopmental disorders, defined by (1) impairments in reciprocal social interaction, (2) impairments in communication skills, and (3) restricted, repetitive and stereotyped patterns of behavior, interests and activities (American Psychiatric Association, 2000). These features may vary in severity and time of onset (Johnson & Myers, 2007). This observation has led to the concept of "autism spectrum disorders" (ASDs) and it includes autistic disorder (childhood autism), Asperger's disorder and pervasive developmental disorder-not otherwise specified (PDD-NOS) (Johnson & Myers, 2007). The exact cause of ASD is unknown (Johnson & Myers, 2007). However, it is evident that ASDs are biologically based neurodevelopmental disorders that are highly heritable (Bailey, Philips, & Rutter, 1996). Research on the causes of ASD has to be extensive, because of the involvement of multiple genes and great phenotypic variation in these disorders (Johnson & Myers, 2007).

1.1.3 Diagnostic classification systems of ASD

Prior to DSM-5 (APA, 2013), which was released in May 2013, ASDs were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (APA, 2000) or the International Classification of Diseases, 10th Revision (ICD-10) (WHO, 1992). In North America, the DSM –IV-TR classification has been used in clinical practice and is the basis for research-standard diagnoses of ASDs, whereas, the ICD-10 is the standard classification system used in clinical practice in Europe and applies the term "pervasive developmental disorders" for ASDs. The subtypes of ASD in each classification system are listed in Table 1, and this table shows how the subtype diagnoses of the two systems correspond.

Table 1 ASD subtype classification

DSM-IV-TR: Autism Spectrum Disorders		***ICD-10:* Pervasive Developmental Disorders**	
Code	**Name**	**Code**	**Name**
299.00	Autistic Disorder	F84.0	Childhood autism
299.10	Childhood Disintegrative Disorder	F84.3	Other childhood disintegrative
299.80	Rett´s Disorder	F84.2	Rett syndrome
299.80	Asperger´s Disorder	F84.5	Asperger syndrome
299.80	Pervasive Developmental Disorder Not Otherwise Specified (Including Atypical Autism)	F84.1 F84.8 F84.9	Atypical autism Other specified pervasive developmental disorder Pervasive developmental disorder, unspecified

The ABC-study, which the current study builds upon, used the DSM-IV-TR diagnostic category of Autistic disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS) and Asperger syndrome. The diagnosis, autistic disorder, is used for children with severe deficiencies within all three symptom domains of ASDs, and the age of onset is by definition before three years of age (APA, 2000). Asperger´s disorder differs from autistic disorder in that there is no significant early delay in language acquisition and cognitive development, and that the symptoms may not become apparent until after three years of age (APA, 2000). For this reason, Asperger´s disorder is often not diagnosed until the child has started school (Johnson & Myers, 2007). The diagnosis of PPD-NOS is used when a child demonstrates severe and pervasive impairments in reciprocal social skills associated with deficits in language skills or with the presence of stereotypic behaviors or restricted interests

or activities, but who do not meet full criteria for autistic disorder or Asperger´s disorder (APA, 2000).

1.1.4 Early detection

Early screening, of all 18- and 24-months-olds, is recommended by the American Academy of Pediatrics, given the potential for early intervention to alter the developmental course of ASDs (Johnson & Myers, 2007). Now, the Modified Checklist for Autism in Toddlers (M-CHAT) is the most frequently used instrument for early screening for ASD (Robins, Fein, Barton, & Green, 2001). However, Stenberg et al. 2014 found that even though one-third of the children who later received an ASD diagnosis were identified through M-CHAT items, the majority scored below cut-off on the screening criteria at 18 months. Their results imply that it might not be possible to detect all children with ASD at this age (Stenberg, Bresnahan, Gunnes et al., 2014).

1.1.5 From subgroupings of ASD to dimensional descriptions

The term autism spectrum disorders (ASDs) was introduced in the 1990s to reflect the broader spectrum of clinical characteristics that defined autism (Johnson & Myers, 2007). Further, a multisite observational study, by Lord, Petkova, & Hus et al. (2012), showed that the subtype diagnoses of ASDs did not have high reliability (Lord et al., 2012). Lord et al., (2012) argue that their findings support the move from existing subgroupings of autism spectrum disorders to dimensional descriptions of core features of social affect and fixated, repetitive behaviors, together with characteristics such as language level and cognitive function (Lord et al., 2012). In the new DSM-5 classification, the diagnosis of autism spectrum disorder, includes the previous diagnoses of autistic disorder, Asperger´s disorder, PDD-NOS, and childhood disintegrative disorder (APA, 2013). The three diagnostic criteria of an autism spectrum disorder is still defined by (1) impairments in reciprocal social interaction, (2) impairments in communication skills, and (3) restricted, repetitive and stereotyped patterns of behavior, interests and activities (APA, 2013). However, the diagnosis of ASD 299.00 (F84.0) have the following specifications: (1) symptom severity levels, on a scale from 1 to 3; (2) whether or not intellectual impairment is present; (3) whether or not language impairment is present; (4) associated with a known medical or genetic condition or environmental factor; (5) other coexisting neurodevelopmental, mental, or behavioral disorders; and (6) whether or not

catatonia is occurring. The purpose of adding the specifiers is to incorporate a dimensional assessment in the diagnosis of ASDs (APA, 2013).

1.1.6 Prevalence

An epidemiological survey of the prevalence of ASD has been carried out in several countries (Fombonne, 2009). The results showed that most studies estimated the prevalence of ASD to be between 0.6 to 0.7% in preschool and school-age children in Europe and North America (Fombonne, 2009). Recent studies from United States (CDC, 2014) and the United Kingdom (Baird, Simonoff, Pickles, Chandler, Loucas, Meldrum, & Charman, 2006) have demonstrated higher prevalence rates, of 1.5 % and 1.2 % respectively. The ASD prevalence is much higher in boys than in girls. Estimates of male-to-female ratios range from 2:1 to 6.5:1 (Johnson & Myers, 2007). The reported prevalence of ASDs in continental Europe, the United Kingdom and the United States has increased by 5- to 10-fold over the past 20 years (Rutter, 2005). Rutter (2005) emphasizes that this increase is largely a consequence of improved assessment and a considerable broadening of the diagnostic concept. However, he claims that a true rise over time in the incidence of ASD cannot be entirely ruled out (Rutter, 2005).

1.1.7 ASD and comorbid psychiatric disorders

The prevalence and incidence rates of psychiatric disorders are higher in people with ASD than in the general population (Mannion, Leader, & Healy, 2013). It has been found that children with ASD frequently have comorbid psychiatric problems (Myers & Johnson, 2007). Among these problems are hyperactivity, inattention, aggression, anxiety, and depression, and medical problems such as epilepsy, and sleep disturbances (Mannion et al., 2013). However, according to Helverschou, Bakken and Martinsen (2011), psychiatric disorders are frequently overlooked in the ASD group and psychiatric symptoms are attributed to the disability itself (Helverschou, Bakken, & Martinsen, 2011). Hence, it is important to identify all of these co-existing problems and the disorders need to be treated according to the same guidelines as for children without ASDs (Myers & Johnson, 2007).

1.2 ASD and anxiety

Anxiety is one of the most common forms of childhood psychopathology. Anxiety disorders are found to be highly prevalent in the normal population (Spence, 1998). However, it has been seen as one of the most difficult areas of child psychopathology to study in representative population samples (Costello, Egger, & Angold, 2005). The main reasons for this are clinical uncertainty about boundaries of the various anxiety disorders (Costello et al., 2005) and the difficulties in distinguishing normal anxiety from pathological anxiety (Pine & Klein, 2008). Pine and Klein (2008) argue that childhood anxieties may be adaptive, however, anxiety may be considered pathological if it limits developmentally appropriate behavior and thus causes functional limitation. Furthermore, Spence (1998) argues that there is evidence that childhood anxiety disorders are not transient phenomena for many children and that, if left untreated, may persist through adolescence and adulthood. Therefore, it is important to examine the developmental trajectory of symptom expression and the potential influencing risk factors.

1.2.1 Diagnostic classification systems of anxiety

According to the DSM-IV-TR (APA, 2000) anxiety disorders include: Panic Disorder, Separation Anxiety Disorder (SAD), Specific Phobia, Social Phobia, Obsessive Compulsive Disorder (OCD), Post-Traumatic Stress Disorder (PTSD), and Generalized Anxiety Disorder (GAD). Table 2 shows the four anxiety subtypes known to be most frequent in preschoolers (Costello et al., 2005).

Table 2 Description of DSM-IV anxiety disorders

Anxiety disorder	Description
Generalized anxiety disorder	Characterized by at least 6 months of persistent and excessive anxiety and worry.
Social anxiety	Characterized by a significant anxiety provoked by exposure to certain types of social or performance situations, which often leads to avoidance.
Separation anxiety disorder	Developmentally inappropriate and excessive anxiety surrounding separation from home or from significant attachment figures.
Specific anxiety disorder	Characterized by a significant anxiety provoked by exposure to a feared object, often leads to avoidance.

1.2.2 Clinical features of anxiety

Anxiety disorders are defined by a more intense experience of anxiety, worry, and apprehension than what is developmentally appropriate (APA, 2000).

Generalized anxiety disorder (GAD) includes multiple worries about a variety of life circumstances (Pine & Klein, 2008). DSM-IV-TR describes that the intensity, duration, or frequency of the anxiety and worry is far out of proportion to actual likelihood or impact of the feared event (APA, 2000). The individual finds it difficult to control the worry and to stop it (APA, 2000). The symptoms of generalized anxiety disorder are restlessness, fatigue, difficulty concentrating, irritability and muscle tension (Costello et al., 2005). Pine and Klein (2008) emphasize that relative to other anxiety disorders, generalized anxiety disorder has very high rates of comorbidity, and it rarely represents on its own in clinic patients. This high comorbidity raises questions about whether the diagnosis identifies an unique syndrome as opposed to a complication of the other associated disorders (Pine & Klein, 2008).

Social anxiety disorder is characterized by anxiety in a range of social situations because of fear of scrutiny, ridicule, humiliation or embarrassment (Pine & Klein, 2008). Some children may not articulate these concerns but feel uncomfortable in social settings. Children must experience discomfort with peers, not only with adults, and anxiety cannot be caused by impaired capacity for socialization, as evidenced by the fact that the children interact satisfactorily with those who are familiar to them (APA, 2000). Pine and Klein (2008) argue that the diagnostic distinction between severe social anxiety disorder and mild pervasive development disorder can be problematic. Chronic avoidance of social interactions might limit development of social competence, contributing to similarities with mild pervasive development disorder. However, in general, children and adolescents with social anxiety desire social contacts, whereas those with pervasive developmental disorder typically lack interest in reciprocal relationships (Pine & Klein, 2008).

Separation anxiety disorder (SAD) is characterized by excessive anxiety concerning separation from the home or from those whom the person is attached (APA, 2000). The anxiety is beyond that which is expected for the individual´s developmental level (APA, 2000) and causes impairment by leading to avoidance (Pine & Klein, 2008). Children with SAD often express fear of being lost and never being reunited with their parents (APA, 2000).

DSM-IV-TR claims that children with SAD tend to come from families that are close knit, and a separation may exhibit social withdrawal, apathy, sadness, or difficulty concentrating on work or play (APA, 2000). One of the eight DSM-IV-TR criteria for fulfilling a SAD diagnosis is difficulties at bedtime and the child may insist that someone stay with them until they fall asleep. This diagnosis is the only anxiety disorder that must begin in childhood (Pine & Klein, 2008).

Specific phobia disorder is defined by marked and unreasonable fear of a specific object that is not intrinsically dangerous, such as animals, or a situation, such as heights (Pine & Klein, 2008). The level of fear is considered extreme, and exposure elicits extreme fear (APA, 2000). In addition, the phobia must either cause clinically significant distress or impair the person´s well-being by leading to interference with ordinary activities because of avoidance (Pine & Klein, 2008).

1.2.3 Assessment and prevalence of anxiety in preschool children

Direct assessment of young children is difficult, because they often lack the cognitive abilities needed to talk about worry, fear, and panic (Dadds, James, Barrett, & Verhulst, 2003). However, a review of epidemiologic literature on anxiety disorders argues that the quality (accuracy, reliability, validity) of instruments used to measure anxiety disorders in the child and adolescent population have improved enormously in the past few years (Costello, Egger, Copeland, Erkanli, & Angold, 2011). Furthermore, Egger and Angold (2004) argue that recent advances in the nosology and diagnosis of psychiatric symptoms and disorders in preschool children have made it possible to begin to define the boundaries between normative anxiety, temperament variation, and clinically significant anxiety disorders in very young children (Egger & Angold, 2004).

Formal meta-analysis of anxiety in preschool children has not been possible because there are too few published studies (Costello et al., 2011). Many epidemiological studies have reported on anxiety in general, without distinguishing among the specific categories set out in, for example, DSM-IV-TR (Costello et al., 2011). However, in recent years, there have been several studies of psychiatric disorders in young children, using newly developed instruments, such as the Preschool Age Psychiatric Assessment (PAPA) (Egger & Angold, 2006) and the Diagnostic Interview Schedule for Children (DISC) (Wood, Piacentini, Bergman,

McCracken, & Barrios, 2002). Prevalence estimates of anxiety, from two community studies which used these interviews, were 6.1% (Briggs-Gowan, Horwitz, Schwab-Stone, Leventhal, & Leaf, 2000) and 9.5% (Costello et al., 2005). Costello and colleagues (2005) reported specific prevalence of the subtypes of anxiety; 2.4% (SAD), 6.5% (GAD), 2.3% (Specific phobia) and 2.2% (Social phobia).

1.2.4 Prevalence of anxiety disorders in ASD

Prevalence estimates for anxiety disorders in ASD range from 10 to 50 % (Szatmari & McConnel, 2011). However, identification of anxiety disorders in individuals with ASD is known to be challenging (Helverschou, Bakken, & Martinsen, 2008). It is argued that there has been a tendency to attribute anxiety symptoms, such as distress symptoms, to the autism condition per se and that anxiety symptoms have been considered less significant than the effect of the disability (Helverschou & Martinsen, 2011; Lainhart, 1999; MacNeil, Lopes, & Minnes, 2009). Helverschou and Martinsen (2011) found that individuals with autism have similar symptoms of anxiety as to non-autistic individuals (Helverschou & Martinsen, 2011). In a review conducted by White, Oswald, Ollendick, and Scahill (2009), anxiety symptoms were found to be among the most commonly observed and impairing symptoms associated with ASD (White et al., 2009).

In another extensive review (2009), MacNeil, Lopes and Minnes found that youth with ASD experience greater levels of anxiety than community populations and similar levels of anxiety to clinically anxious groups, and different patterns of anxiety when compared to other clinical groups. Among these studies, a follow up-study (2000) revealed that children and adolescents with ASD scored higher than community–based norms on a measure of generalized and separation anxiety (Kim, Szatmari, Bryson, Streiner, & Wilson, 2000). Sukhodolsky, Shahill, and Gadow (2008) also found a significant relationship between ASD and generalized anxiety and separation anxiety.

Among all the reviewed studies, the only study conducted on preschool children (2005) indicated that teachers rated children with ASD as having more severe anxiety symptoms than the non-ASD group (i.e., Generalized anxiety disorder, Social phobia, Specific phobia and compulsions) (Weisbrot, Gadow, DeVincent, & Pomeroy, 2005). However, the same study indicated that parents rated the non-ASD children as higher than ASD children on several anxiety symptoms (i.e., Separation anxiety, Generalized anxiety disorder).

Anxiety is not considered a phenomenological characteristic of ASD. However, anxiety in ASD is of particular interest because it has been hypothesized to be closely knit to the core symptoms. Sukhodolsky et al., (2008) argue that "insistence of sameness" could be seen to be a reflection of anxiety. It has been observed that changes in routines and interruption of stereotyped behaviors may increase anxiety, tension, and emotional upset in children with ASD (Sukhodolsky et al., 2008). In one of Kanner´s (1947) case-stories, he described a child with autism as following:

> *«It was observed at early time that he was happiest when left alone, almost never cried to go to his mother, did not seem to notice his father´s homecomings, and was indifferent to visiting relatives." (Kanner, 1947)*

This description shows a lack of interest in reciprocal relationships. Some children with Asperger syndrome lack insight into their social and emotional problems (Attwood, 2000). However, many individuals with ASD are intensely aware of their lack of social connectedness (Attwood, 2000). This awareness of their social disability may logically generate anxiety. And a co-occurring anxiety disorder may increase the overall social impairment associated with ASD (White et al., 2009). Thus, anxiety may have bidirectional effects with the social disabilities of ASD. For these reasons, White et al. (2009) argue that a developmental approach is needed to understand how anxiety develops in children with ASD and how it may interact with the core disabilities of ASD. According to Lord and colleagues (2005), there is an urgent need for the development of effective approaches to assess and treat children with ASD (Lord, Wagner, Rogers, et al., 2005). Whereas there are few published studies of anxiety in typically developing preschool children, there is also limited research on anxiety in preschool children with ASD.

1.3 ASD and sleep problems

In recent years, there has been an increasing interest in the role of sleep in the first years of life, both in the general population and among children with ASD. Gregory and Connor (2002) claim that sleep is fundamental for the physical, cognitive, and emotional development in infants and children (Gregory & Connor, 2002). Dahl and Harvey argue that there is increasing evidence that sleep has an important role in basic aspects of learning and memory consolidation, as well as impacting on the regulation of behaviors and emotions (Dahl & Harvey, 2008). Therefore, it is suggested that inadequate or disturbed sleep in childhood and adolescence may have long-term consequences on learning and the development of self-regulation with major clinical implications for child and adolescent psychiatry (Dahl & Harvey, 2008).

1.3.1 Classification of sleep problems

In previous research, most measurements have focused on frequency and duration of night waking, and/or sleep onset difficulties, which are the most common sleep concerns of parents (Gaylor, Goodlin-Jones, & Anders, 2001). A clinical review article by Richdale and Schreck (2009), examined the research literature on sleep problems in ASDs. They confirm that there is no clear consensus of what defines a sleep disorder (Richdale & Schreck, 2009). Researchers typically construct their own criteria or definitions of sleep problems, such as cut-off or frequency scores on sleep questionnaires or diaries, or based on parent-report that a sleep problem is present (Richdale & Schreck, 2009). Despite the lack of definitions, researchers claim that sleep problems characterized by abnormalities in quantity, quality or timing of sleep are the most common types of sleep disturbances affecting young children with or without pervasive developmental disorder (DeVincent, Gadow, Delosh, & Geller, 2007; Patzold, Richdale, & Tonge, 1998; Wiggs & Stores, 2004). Brief awakenings during the night are typical through the first 18 months of life. However, both the frequency and length of night-time awakenings tend to decrease with age (Sadeh & Anders, 1993).

Furthermore, DSM-IV-TR provides a distinction between primary sleep disorders on the one hand and those which occur secondary to another psychological condition, a medical condition or substance use on the other (APA, 2000). Table 3 shows an overview of some of

the primary sleep disorders classified in DSM-IV-TR which are examined in the current study.

Table 3 Description of diagnoses of sleep problems used in the current study

Sleep disorder	Description
Dyssomnias:	
Sleep Onset Insomnia	Characterized by difficulties initiating sleep
Night Awakening Insomnia	Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings
Parasomnia:	
Night terror	Characterized by feelings of terror or dread, the child appears extremely frightened and agitated, while screaming. The child is not awake and is difficult to sooth. Night terrors occur in Stage 4 NREM sleep.

1.3.2 Clinical features of sleep problems

Insomnia is characterized by difficulties falling asleep and/or maintaining sleep, or poor quality of sleep (APA, 2000). These difficulties are by far the most common sleep problems in preschool children (Carr, 2006). Carr (2006) claims that many children have settling and night-waking problems from birth, however, others develop them following some precipitating event or set of circumstances. Furthermore, such precipitating factors may be biological (i.e. serious illness or injury) or psychosocial (i.e. stressful life events, an insecure mother-infant attachment) (Carr, 2006). As for parasomnia, night terrors are often mistaken for night-mares (Carr, 2006). Night terrors are distinct different from night-mares, and are characterized with the child sitting up in bed and screams loudly or bolts out of bed and moves frantically, as if trying to escape (Carr, 2006). During a night terror, the child looks terrified, is hyper-aroused, and is unresponsive to comforting (Carr, 2006). In contrast to nightmares, the child rarely recalls any details from a dream when awaking from a night terror (Carr, 2006).

1.3.3 Prevalence of sleep problems in ASDs

A recent study found that sleep problems are common in childhood, occurring in 25-40% of typically developing (TD) children (Hodge, Carollo, Lewin, Hoffman, & Sweeney, 2014). In addition to the core symptoms of social/communication deficits and a restricted repertoire of

behaviors, children with ASD often experience sleep problems (Wiggs & Stores, 2004). Humphreys et al., (2014) reported that children with autistic spectrum disorders (ASDs) are likely to have more disturbed sleep than typically developing children (Humphreys et al., 2014). Parental surveys have indicated a 50-80% prevalence of sleep problems in children with ASD, compared with a 9-50% prevalence rate in age-matched, typically developing children (Kotagal & Broomall, 2012). Another recent study found that 80% of children and adolescents with ASD had sleep problems (Mannion, Leader & Healy, 2013). Compared with typical controls, children with ASD have more trouble falling asleep, wake up more during the night, wake up earlier in the morning, and sleep less (Allik, Larsson, & Smedje, 2006b; Couturier, Speechley, Steele, Norman, Stringer & Nicholson, 2005; Krakowiak, Goodlin-Jones, Hertz-Picciotto, 2008; Mayes, Calhoun, Bixler, & Vgontzas, 2009; Patzold et al., 1998; Richdale & Prior, 1995). According to the findings of Miano and Ferri (2010) insomnia is the most common sleep concern in ASD (Miano & Ferri, 2010). Mayes and Calhoun (2009) and other studies of children with autism have found a significant relationship between sleep problems and autism severity, behavioral problems, hyperactivity and affective problems (DeVincent et al., 2007; Liu, Hubbard, Fabes, & Adam, 2006; Malow, Marzec, McGrew, Wang, Henderson & Stone, 2006; Mayes & Calhoun, 2009; Patzold et al., 1998; Schreck, Mulick, & Smith, 2004). Fewer hours of sleep per night seems to predict overall autism scores and social skills deficits (Schreck et al., 2004).

1.3.4 Neurobiology of ASD and sleep

A review conducted by Johnson, Gianotti and, Cortesi (2009) claims that several neurotransmitter systems involved in promoting sleep and establishing a regular sleep-wake cycle are affected by ASD. These neurotransmitter systems include gamma-aminobutyric acid (GABA), serotonin, and melatonin (Johnson et al., 2009). A systematic review and meta-analysis, conducted by Rossignol and Frye (2011), it is argued that children with ASD have reduced levels of circulating melatonin and abnormal melatonin circadian rhythm (Rossignol & Frye, 2011). Furthermore, Johnson et al., (2009) argue that the abnormalities in production, found in neurotransmitter systems, along with evidence of clinical sleep and circadian disturbances, provide evidence for involvement of the neurobiological networks regulating sleep in individuals with ASD (Johnson et al., 2009).

1.3.5 A biopsychosocial model of sleep in ASD

Sikora, Johnson, Clemons and, Katz (2012) argue that ASD is an independent risk factor for sleep problems (Sikora et al., 2012). However, Humphrey et al. (2014) claim that the aetiology of sleep disorders in ASD is poorly understood and is likely due to multiple complex interactions between biological, psychosocial, behavioral and environmental factors (Humphreys et al., 2014). According to Richdale and Schreck (2009), an examination of potential precipitating or predisposing factors is best considered from a biopsychosocial viewpoint (Richdale & Schreck, 2009). Richdale and Schreck (2009) have presented a biopsychosocial model (See figure 1) of sleep in ASD with two-way arrows indicating potential reciprocal interactions among ASD contributors and symptoms and sleep problems. Sleep problems may occur as a result of: 1) intrinsic biological or genetic abnormalities that alter architecture or biochemistry; 2) psychological or behavioral characteristics connected with core or associated features of ASDs; or 3) factors in the family home or environment, including child rearing practices that do not promote good sleep (Richdale & Schreck, 2009).

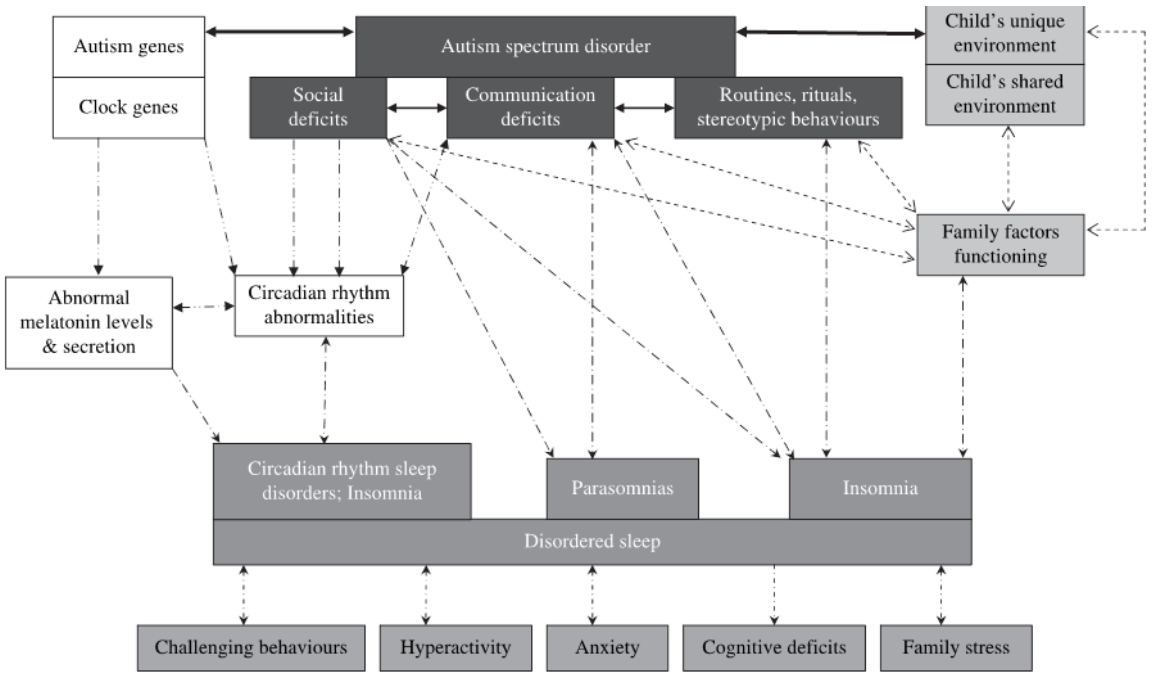

Fig. 1. A biopsychosocial model of common sleep problems and the core behaviours in autism spectrum disorders.

Figure 1 A biopsychosocial model of common sleep problems and the core behaviors in autism spectrum disorders (Richdale & Schreck, 2009).

According to Richdale and Schreck´s (2009) understanding, any one, or combination of these three factors, may contribute to sleep problems in the children with ASD. They also emphasize that this complex interaction between biological, psychological and social/environment factors is an important consideration for investigation and treatment of sleep difficulties in ASD (Richdale & Schreck, 2009). However, with this model in mind, the current study will focus merely on the relationship between ASD, sleep problems and anxiety.

1.3.6 The importance of sleep in preschool children with ASD

In Carr´s (2006) contextual approach in understanding insomnia, he argues that families, where children have sleep problems, may experience further difficulties that may compound sleep problems. Parents become sleep-deprived and exhausted, which again may have serious consequences for the child and it´s siblings, and the marital relationship (Carr, 2006). Furthermore, Dahl and Harvey (2008) argue that it is important to recognize that even simple and seemingly minor behavioral sleep problems can become a source of major distress and conflict for children and their families, and these can have serious health consequences (Dahl & Harvey, 2008). We know from studies of the adult general population that chronic sleep problems have severe impact on both quality of life and physical and mental health (Taylor, Lichstein, Durrence, Reidel, & Bush, 2005; Taylor, Mallory, Lichstein, Durrence, Reidel & Bush, 2007). Thus, sleep problems in children with ASD will most likely influence both the children and their families even stronger, as they are already affected by severe symptoms of ASD. In addition, there are studies indicating that insomnia in itself aggravates the autistic symptoms (Allik, Larsson, & Smedje, 2006a; Schreck et al., 2004; Sivertsen, Posserud, Gillberg, Lundervold, & Hysing, 2012). Mannion and Leader (2013) emphasize the extreme importance of identifying and treating sleep problems, as they may influence the effectiveness of daytime interventions. The parents of a child with ASD are under high levels of stress related to their child´s disorder (Richdale & Schreck, 2009). Sleep difficulties may have an added negative impact on family functioning and parent psychological well-being (Sikora et al., 2012). Johnson et al., (200) argue that addressing sleep problems in children with ASD, may improve daytime behavior, but also the parent´s functioning.

1.4 ASD, anxiety and sleep problems – previous research

The literature on the relationship between sleep problems and ASD among preschool children with anxiety disorders is limited. However, it has been suggested that emotional and behavioral problems are related to sleep problems in children with ASD (Richdale, 1999; Sivertsen et al., 2012). Anxiety is known to be accompanied by physiological and cognitive arousal (El-Sheikh, Buckhalt, Keller, & Granger, 2008), neither of which provides a basis for restful sleep. Mayes and Calhoun (2009) found that sleep problems were not related to age, IQ, gender, race, parent occupation, neuropsychological functioning or learning ability. However, sleep problems increased with severity of autistic symptoms and with severity of parent reported symptoms (Mayes & Calhoun, 2009). These symptoms were oppositional behavior, aggression, explosiveness, attention deficit, impulsivity, hyperactivity, anxiety, depression and mood variability (Mayes et al., 2009). Rzepckas, McKenzie, McClure and, Murphy (2011) found significant positive correlations between sleep problems and anxiety, indicating that higher levels of sleep problems are associated with higher levels of anxiety in children with intellectual disability (ID) and/or ASD (Rzepecka et al., 2011).

However, these studies have several limitations. A potential problem in studies relying only on parent ratings, to investigate the relationship between sleep problems and comorbid symptoms, is common source variance, rater bias, and halo effects. Parents may tend to rate all items relatively high or low, thus spuriously inflating the relationship between the subscale scores (Rzepecka et al., 2011). Mayes and Calhoun (2009) postulates that research studies should use multiple sources and symptom measures whenever possible because of the potentially confounding effect of common source variance (Mayes & Calhoun, 2009). The study of Rzepckas et al (2011) used the Child's Sleep Habits Questionnaire (CSHQ) (Owens, Spirito, & McGuinn, 2000) and the Spence Children's Anxiety Scale-Parental Version (SCAS-P) (Nauta, Scholing, Rapee, Abbott, Spence, & Waters, 2004). These questionnaires are, however, not designed or specifically validated for children with ASD.

1.4.1 The direction of the association between sleep problems and emotional problems

The direction of the association between sleep and emotional problems is unclear. Sleep problems may affect emotional state at daytime and/or emotional problems may affect sleep patterns such as rumination at bedtime for anxious children (Hysing, Sivertsen, Stormark, Elgen, & Lundervold, 2009). Sadeh and Anders (1993) argue that bedtime and falling asleep may represent a separation from the parent and from the "world" for the infant. Thus, this might generate anxiety symptoms in infants in ASD. It is proposed that the association between sleep and other problems may not be unidirectional or causal (Mayes et al., 2009). Behavior problems may cause sleep problems and vice versa. However, Sikora et al. (2012) emphasize the bidirectional relationship between sleep and daytime behavior, suggesting there could be other factors that influence both. For example, having a neurodevelopmental disorder might not only result in core ASD symptoms, but also impaired behavior and regulation of sleep (Sikora et al., 2012). ASD symptoms, such as a lack of social awareness or non-functional routines, may impact on both sleep and daytime behavior.

Thus, it is important to examine the direction of association between ASD, sleep and anxiety. Using a longitudinal approach it is possible to detect a potential developmental pathway to anxiety in preschool children with ASD. Given the importance of sleep in infants, this approach makes it possible to detect risk factors (i.e. sleep problems) as well as vulnerability factors (i.e. ASD).

1.4.2 Development of psychopathology – Predicting emotional problems

The current study builds upon the perspective of developmental psychopathologists. Cicchetti (2006) describes developmental psychopathology as:

> *"An evolving scientific discipline focusing on explaining the interplay among the biological, psychological, and social-contextual aspects of normal and abnormal development across the life span. (….) Developmental psychopathologists do not work from a particular theory, however they seek to integrate knowledge across scientific disciplines at multiple levels of analysis and within and between developmental domains"* (Cicchetti, 2006, p. 1).

Rutter argues that key life turning points may be times when the presence of protective mechanisms could help individuals redirect themselves from a risk trajectory onto a more adaptive developmental pathway (Rutter, Kim-Cohen, & Maughan, 2006). Likewise, Toth and Cicchetti (1995) argue that these periods of developmental transition may also be times when individuals are most amenable to profiting from therapeutic interventions (Cicchetti & Toth, 1995). Hence, early sleep problems may forecast behavioral/emotional problems, and there may be important developmental change in the overlap between sleep problems and behavioral/emotional problems (Gregory & O´Connor, 2002). Gregory and O´Connor (2002) argue that sleep problems constitute an important correlate and risk factor for psychopathology in adults, but their psychopathological significance in children is much less clear (Gregory & O´Connor, 2002). Rutter et al. (2006) claim that there is a pronounced need for knowledge on early predictors, and longitudinal relations between predictors contributing to development of emotional problems (Rutter, Kim-Cohen, & Maughan, 2006). Predictors may act as either risk factors, protective factors, promotive factors or vulnerability factors (Carr, 2006), and they may act through both mediating and moderating processes (Baron & Kenny, 1986).

1.4.3 Implications

Richdale and Schreck (2009) claim that the influence of sleep problems on daytime behaviors is largely neglected (Richdale & Schreck, 2009). In addition, Gregory and O´Connor (2002) argue that sleep problems constitute an important correlate and risk factor for developing psychopathology. Sikora et al. (2012) also emphasize the need for documenting that internalizing behavior is related to a child´s sleep habits, because internalizing behaviors often are problematic for children with ASD (Sikora et al., 2012).

Based on the above considerations, the current study may contribute to the understanding of development of anxiety in children with ASD. The aims and the hypotheses are presented in the following section.

1.5 Aims of the current study

Prevalence estimates for anxiety disorders in children with ASD have shown that there is a relationship between anxiety and ASD. In addition, parents of children with ASD frequently report that their children have sleep disturbances. However, studies of anxiety in preschool children are few and there are several limitations in the previous studies. Among the limitations are the lack of validated diagnostic interviews, subjects withdrawn from clinical treatment studies, ASD diagnoses which were not generated from autism diagnostic criteria, small sample sizes and most of the studies examine children older than 6 years.

The current study uses a prospective longitudinal approach to examine the relationship sleep problems and ASD in preschool children with subtypes of anxiety disorders. The method provides a predictive opportunity to look at sleep problems in early age, as a potential mediating factor on the relationship between ASD and anxiety. The diagnoses are clinically validated and the parent interviews have high inter-rater reliability. According to the existing literature, no research has previously been conducted on the potential mediating role of sleep problems on the relationship between ASD and anxiety.

The aim of the current study is to examine the relationship between early age sleep problems and ASD among preschool children with anxiety disorders. The specific aims are:

(1) to examine the relationship between ASD and subtypes of anxiety; generalized anxiety, social anxiety, separation anxiety and specific anxiety.

(2) to examine the relationship between ASD and sleep problems, among these are the diagnoses of insomnia characterized by nocturnal awakenings, sleep onset delay, night terror.

(3) to examine whether sleep problems at 18 months and 36 months of age mediates the relationship between ASD and subtypes of anxiety, in children 3-5 years of age.

The current study´s main hypotheses are:

(1) There is a significant relationship between ASD and subtypes of anxiety in preschool children.

(2) There is a significant relationship between an ASD diagnosis at 3-5 years and sleep problems at 18 months and 36 months. Children with ASD have higher prevalence of insomnia than typically developing children.

(3) The significant relationship between ASD and anxiety can be accounted for by the mediating role of sleep problems in children with ASD.

2 Method

2.1.1 The Autism Birth Cohort (ABC) Study

The current study used data collected in the Autism Birth Cohort Study (ABC-study) (Stoltenberg , Schjolberg, & Bresnahan et al., 2010) and the Norwegian Mother and Child Cohort Study (MoBa) (Magnus, Irgens, & Haug et al., 2006). The ABC-study is a case-cohort study of autism spectrum disorders nested within MoBa. MoBa is a large population-based, prospective pregnancy cohort started by the Norwegian Institute of Public Health (NIPH) for studying causes of disease in mothers, fathers, and children (Magnus et al., 2006). MoBa recruited participants from 1999 to 2009 from various birth clinics in Norway and the cohort now includes 114 516 children (Súren, 2014). Mothers in the MoBa cohort answer questionnaires during pregnancy, and at given intervals after the child's birth (the questionnaires so far are: 15th, 22nd and 30th week of pregnancy, 6-, 18- and 36-months after birth and at 5-, 7- and 8 years of age). The ABC-study aims to investigate causes of autism and examine how ASD develops in children (Stoltenberg et al., 2010). It is designed and managed in collaboration between NIPH and the Mailman School of Public Health at Columbia University in New York (Súren, 2014). The clinical assessment in the ABC study is cross-sectional, inviting children once for a developmental and diagnostic assessment by Nic Waals Institute in Oslo. The data collection is funded by the National Institute of Neurological Disorders and Stroke, and some of the research activities in Norway are funded by the Research Council of Norway and the Regional Health Authority of Southeastern Norway (Surén, Roth, Bresnahan et al. 2013).

2.1.2 Case identification in the ABC Study

Potential cases of ASDs and a random sample of controls were invited to participate in the study (Stoltenberg et al., 2010). ASD cases have been identified through (1) questionnaire screening when the child is 36 months (2) professional and parental referrals of children suspected of having ASDs, and (3) linkage to the Norwegian Patient Register (NPR) (Surén et al. 2013). The screening at 36 months was based on the Social Communication Questionnaire (Berument, Rutter, Lord, Pickles, & Bailey, 1999). An overview of the case-finding mechanisms is provided in Figure 2 (Surén, 2014).

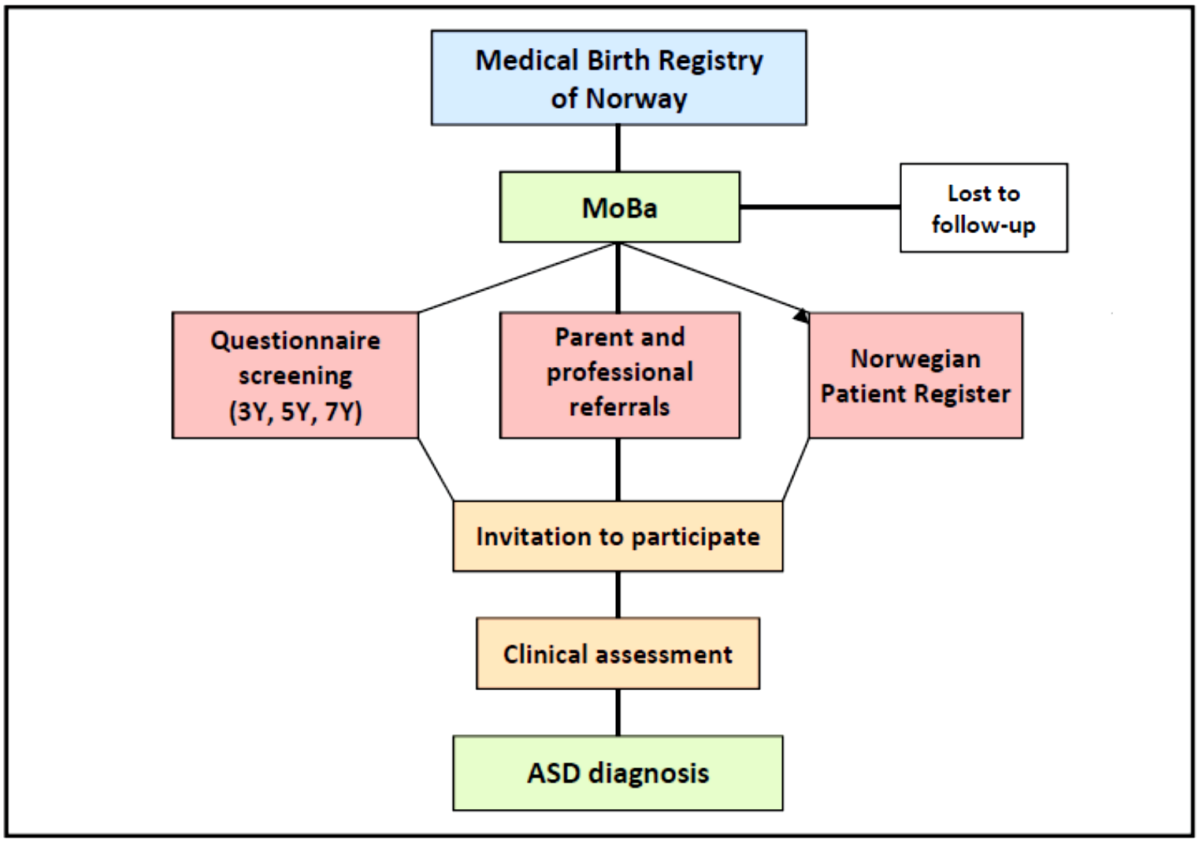

Figure 2 Case identification in the ABC Study (Surén, 2014)

2.1.3 The assessment at the ABC-clinic

When a child with ASD or potential ASD was detected through any of the mechanisms described in the case identification section, he/she was invited to participate in a clinical assessment that included standardized diagnostic, cognitive, and behavioral instruments (See table 4 for descriptions).

Table 4 Overview of the standardized instruments, used in the clinical assessment of children 3-5 years old

Instruments	Type of measure
Autism Diagnostic Interview, Revised (ADI-R)	Semi-structured, standardized diagnostic interview
Autism Diagnostic Observation Schedule (ADOS)	Semi-structured assessment of communication, social interaction, and play or imaginative use of materials
Stanford-Binet Intelligence Scales, 5th ed. (SB-5)	Standardized test of intelligence and cognition
Vineland Adaptive Behavior Scales (VABS) (Communication Domain only)	Assessment of receptive, expressive, and written communication skills
The Mullen Scales of Early Learning (Mullen)	Assessment of fine and gross motor skills
Preschool Age Psychiatric Assessment (PAPA)	Diagnostic interview of psychiatric disorders

The primary diagnostic tools were the research standard instruments for diagnosis of autism spectrum disorders, the Autism Diagnostic Interview – Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord, Risi, Lambrecht, et al., 2000). These are shown to have high reliability and validity in making diagnoses of autism spectrum disorders in children (Lord et al., 1994; Lord et al., 2000). Diagnostic conclusions were best-estimate clinical diagnoses derived from test and interview results and from information collected from parents and teachers (Surén, Stoltenberg, Bresnahan, et al., 2013). Diagnoses were based on DSM-IV-TR (APA, 2000) criteria, and the case definition included codes 299.00 (Autistic Disorder), 299.80 (Asperger`s Disorder), and 299.80 (PDD-NOS).

2.2 Participants

In the current study, clinical data from the ABC-study and longitudinal data from MoBa were used. The sample of 490 children was all preschool children, who had participated in the clinical assessment in the ABC clinic and where the mothers had completed the 18 and 36 months questionnaires. The sample consisted of 306 boys and 184 girls. To examine the whole spectrum of autism spectrum disorders, Autistic disorder, Asperger syndrome, PDD-NOS, sub-threshold autistic disorder, sub-threshold Asperger syndrome, and sub-threshold PDD-NOS were included. The total number of participants who were assessed, but did not receive a diagnosis was 194. 75 children received a diagnosis within the autism spectrum and 221 received another neurodevelopmental diagnosis (e.g mental retardation, language disorder).

2.3 Instruments

The ABC-study included many different instruments for assessing the child´s development. The following gives merely a description of the instruments used in the current study.

2.3.1 Interview

The Preschool Age Psychiatric Assessment (PAPA) (Egger & Angold, 2004) is a structured interview with the purpose of identifying problems areas or, where relevant, diagnosing psychiatric disorders in children aged 2 to 5 years. The PAPA provides a reasonably reliable

standardized measure of DSM-IV psychiatric symptoms and disorders in preschoolers for use in both research and clinical service evaluations of preschoolers as young as 2 years old (Egger et al., 2006). PAPA-derived diagnoses are consistent with diagnoses in the diagnostic systems DSM-IV (Lipkin, Stoltenberg, Susser, et al.,, 2010). When administering the interview, interviewers ask a series of mandatory probe questions for each section. The answers to these probe questions inform the interviewer as to whether to proceed with the section. These may be supplemented by discretionary probe questions when the information gathered through the initial probe questions is deemed by the interviewer to be inadequate to render a decision as to whether or not to proceed. Most data in the PAPA are obtained for the three-month period preceding the interview. The clinical assessments in the ABC Study have been substantially shortened over the course of the study. The PAPA was used in the ABC-Study from 2005-2008 (Lipkin et al., 2010).

In the current study, inclusion in an anxiety group was defined by presence of one or more of DSM-IV-TR symptom(s) of anxiety or worry that had persisted for 3 months or longer. The four anxiety subtypes known to be most frequent in preschoolers (Costello, Egger, & Angold, 2005) were included: (a) Symptoms of specific phobia is an anxious response to the presence or anticipation of a specific object or situation. (b) Symptoms of social anxiety were reported when the child showed fear of one or more social or performance situation(s), which had to be present in peer settings. (c) Symptoms of separation anxiety disorder (SAD) involved items on excessive anxiety concerning separation from home or from caregiver(s). (d) Symptoms of generalized anxiety disorder (GAD) required extensive anxiety and worry occurring more days than not and had to be accompanied by at least one additional symptom (restlessness, easily fatigued, difficulty concentrating or muscle tension). Questions on sleep were excluded from the diagnosis of generalized anxiety disorder.

Based on information obtained in the PAPA interviews, diagnoses of insomnia and parasomnia were derived according to DSM-IV-TR criteria (APA, 2000) and Anders criteria (Gaylor, Goodlin-Jones & Anders et al., 2001). In DSM-IV-TR, insomnia constitutes difficulties initiating or maintaining sleep or non-restorative sleep. The DSM-IV-TR criteria do not quantify what length of time before falling asleep which qualifies for an insomnia symptom and do not specify a frequency of insomnia symptoms (i.e., times per week) during an episode of insomnia. Based on the DSM-IV-TR though, Gaylor et al (2001) have developed a classification of dyssomnias in younger children making a distinction among

perturbation, disturbance, and disorder (Gaylor et al., 2001). Perturbation is a part of normal development where interventions are not needed. Disturbances are considered "risk conditions". The assumption is that if no intervention occurs, it may likely progress to a disorder. Disorders are considered more serious and require more active, therapeutic intervention (Gaylor et al., 2001). According to their classification, using more than 20 minutes to fall asleep 5 to 7 times a week for at least 1 month signifies a sleep onset disorder for children older than 24 months. Based on the DSM-IV-TR criteria, the current study divided definitions of insomnia in sleep onset delay and nocturnal awakenings. Both qualify for an insomnia disorder. Sleep onset delay-insomnia was defined as more than 20 minutes to fall asleep 5 to 7 times a week for at least 1 month or using sleep medication. Nocturnal awakenings-insomnia was defined as 5 or more awakenings (duration $\geq$ 10 minutes) a week for at least 1 month. Qualification of parasomnia, defined by night terror, was fulfilled if presence of episodes during sleep, where the child is not awake or conscious, but seems terrified and screams. The child has no memories from the incident. (See appendix for the computerized algorithms of insomnia and parasomia diagnoses).

2.3.2 Inter-rater reliability

Trainees completed a workshop lasting for 2 days (Lipkin et al., 2010). At first, trainees reviewed two video-taped interviews from the video-training package from Angold and Eggers group, with direct training provided by Ed Potts, as well as video-taped assessments from the ABC clinical assessments. Volunteer parents were interviewed by the PAPA trainer, and trainees scored the interview items independently. The trainees had to complete at least three interviews by themselves with a reliable, and study trained staff, achieving at least an agreement of 0.80 on all items that rate if a symptom is present or not. After each interview, the trainer and trainee discussed the individual scores from the interview and calculate the percent agreement items agreed upon. During the training phase, all testers/interviewers double-scored three tests/interviews with a fully-trained staff member. Reliability was calculated, and discrepancies were resolved through discussions and reviews of test/interview manuals. Before conducting any interviews independently, a trainee had to complete another three live interviews / tests under close supervision of a senior study trained staff member and achieve instrument – specific reliability (Lipkin et al., 2010).

2.3.3 Questionnaires

The current study used data from the MoBa Questionnaires at 18 and 36 months (NIPH, MoBa) which were completed by the mother of the child (See Appendix for excerpts of the questionnaires).

Sleep problems (18 and 36 months)

The MoBa questionnaires contain information of whether the child has a sleep problem or not. If the respondents answered positive this was defined as having sleep problems. This method has previously been applied in the Bergen Child Study (Hysing et al., 2009; Sivertsen, Hysing, Elgen, Stormark, & Lundervold, 2009; Sivertsen et al., 2012).

Scales of anxiety (18 and 36 months of age)

The MoBa questionnaires contain an extract of questions from The Achenbach System of Empirically Based Assessment (ASEBA); the Child Behavior Checklist for Ages 1 ½-5 (CBCL) (Achenbach, Rescorla, McConaughey, Pecora, Wetherbee & Ruffle, 2003). The CBCL is a widely used questionnaire consisting of 118 items, assessing emotional and behavioral problems in children. The scales have demonstrated reliability and validity: test–retest stability (.89) and internal consistency (.90) (White & Roberson-Nay, 2009). In the current study, two scales of anxiety were derived from the anxious/depressed syndrome dimension in CBCL, at 18 and 36 months of age. The scales of anxiety at 18 and 36 months had a Cronbach´s alpha of .75 and .60 (See table 5). It is important to notice that all questions concerning sleep in CBCL are excluded from the anxiety scale.

Table 5 Child Behavior Checklist, Anxiety subscales descriptions, 18 and 36 months

	No. of items	Cronbach´s	Description
Anxiety scale (18 months)	3	.75	Clings to adults or too dependent; Gets upset when separated from parents; Can´t concentrate; Can´t pay attention for long
Anxiety scale (36 months)	6	.60	Afraid to try new things; Clings to adults or too dependent; Gets upset when separated from parents; Too fearful or anxious; Get distressed when you go out and he/she is going to be looked after by family or a babysitter he/she knows; Comes over to you when something that makes him/her anxious

2.4 Ethical considerations

2.4.1 Consent

Participation in MoBa and the ABC Study is based on written informed consent from the mother (Súren, 2013). To participate in the clinical assessment of the ABC Study, an additional written informed consent was received from the mother (Súren, 2014). The MoBa consent is a so-called broad consent (Súren, 2014). A broad consent is characterized as an agreement of the participants to provide biological materials and questionnaire data for use in a wide variety of research projects (Sheehan, 2011).

2.4.2 Information to the participants

Information about the types of on-going research projects was given to participants. In addition, they were reminded that participation is voluntary and that they had the right to withdraw if they wanted to (Súren, 2014). The participants, in MoBa, who were invited to the clinical assessment in the ABC Study, received a separate invitation brochure. This brochure contained information about the scientific rationale for the study, the collaborators involved, and the content of the clinical assessment (Surén, 2014).

2.4.3 Legal permits

MoBa and the ABC Study are approved by the Regional Committee for Medical and Health Research Ethics for Southeastern Norway (REK) and have permits from the Norwegian Data Inspectorate (Surén et al., 2013).

2.5 Statistical analyses

To test the hypotheses, binary logistic regression analysis was used in order to follow the principles of mediation analysis (Baron & Kenny, 1986). At step 1 it was assessed whether the predictor ASD (independent variable) had an impact on each subtype of anxiety disorder (dependent variable); generalized anxiety, social anxiety, separation anxiety and specific anxiety. At step 2 it was assessed whether the predictor ASD had an impact on sleep problems (mediator variable) at 18 and 36 months. At step 3 it was assessed whether the predictor sleep problems at 18 months and 36 months had an impact on each of the subtypes of anxiety. At step 4, the relation between ASD and subtypes of anxiety was examined once again, now with the mediator included in the analysis. Analyses were done using SPSS version 20.0 (IBM Corp., 2011)

2.5.1 Mediation analysis

To test a theory of mediation, a significant relationship between the independent and the dependent variable has to occur. This is important for determining (1) whether to proceed with analyses of mediation and (2) whether a proposed mediator fully or partially accounts for an effect (Rucker, Preacher, Tormala, & Petty, 2011). According to Baron and Kenny (1986), a given variable may be said to function as a mediator to the extent that it accounts for the relation between the predictor and the criterion (Baron & Kenny, 1986). To clarify the meaning of mediation, a path diagram is shown in figure 3.

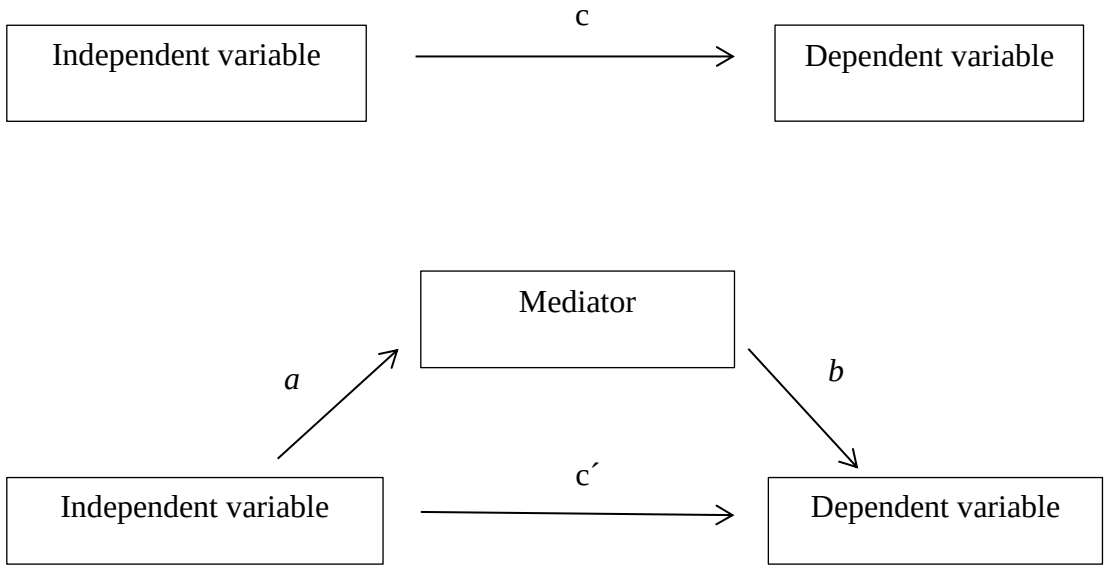

Figure 3 Path diagram of the mediation analysis

The model of Baron and Kenny (1986) assumes a three-variable system. There are two causal paths feeding into the outcome variable: the direct impact of the independent variable (Path c) and the impact of the mediator (Path b). There is also a path from the independent variable to the mediator (Path a) (Baron & Kenny, 1986). A variable function as a mediator when it meets the following conditions: Firstly, variations in the levels of the independent variables significantly account for variations in the presumed mediator (i.e., Path *a*). Secondly, variations in the mediator significantly account for variations in the dependent variable (i.e., Path *b*). Lastly, when Paths a and b are controlled, the effect of the independent variable is reduced and the effect of the mediator remains significant (Baron & Kenny, 1986). The strongest demonstration of mediation occurs when Path *c* is zero (Baron & Kenny, 1986).

3 Results

In the following section the results from the statistical analysis will be presented.

3.1 Sample characteristics

Data was available for 490 children. The total number of participants who were assessed, but did not receive any diagnosis was 194. 75 children received a diagnosis within the autism spectrum and 221 received another neurodevelopmental diagnosis (e.g mental retardation, language disorder). Among children with ASDs, the prevalence of generalized anxiety disorder was 17.3%, separation anxiety 21.6%, social anxiety 6.7% and specific anxiety 25.8%. The prevalence of any anxiety was 49.3% in the ASD group, 40.7% in the No Diagnosis group and 46.1% in the Other Diagnosis group. The prevalence of generalized anxiety was higher among children with ASD (17.3%, $p < .035$) than in the groups with No Diagnosis (8.2%) and Other Diagnosis (13.1%). The sample contained 306 boys and 184 girls. Table 6 shows an overview of the characteristics of the predictors and the subtypes of anxiety disorders.

Table 6 Sample Characteristics: Predictors byAnxiety Disorders

	Generalized Anxiety Frequency	Separation Anxiety Frequency	Social Anxiety Frequency	Specific Anxiety Frequency	Total Frequency
Groups included					
No Diagnosis[1]	16 (8.2%)	22(29.3%)	7 (9.3%)	28 (37.3%)	194
ASD[2]	13 (17.3%)	42 (21.6%)	13 (6.7%)	50 (25.8%)	75
Other Diagnosis[3]	29 (13.1%)	55 (24.9%)	22 (10.0%)	66 (29.9%)	221
Total	58 (11.8%)	119 (24.3%)	42 (8.6%)	144 (29.4%)	490
Sleep problem 18 months					
No	51 (11.0%)	111 (23.9%)	36 (7.8%)	132 (28.4%)	464
Yes	7 (26.9%)	8 (30.8%)	6 (23.1%)	12 (46.2%)	26
Sleep problem 36 months					
No	49 (10.7%)	110 (24.0%)	38 (8.3%)	131 (28.6%)	458
Yes	9 (28.1%)	9 (28.1%)	4 (12.5%)	13 (40.6%)	32
Sex					
Boy	41 (13.4%)	78 (25.5%)	25 (8.2%)	95 (31.0%)	306
Girl	17 (9.2%)	41 (22.3%)	17 (9.2%)	49 (26.6%)	184
	Mean (SD)				
Anxiety 18 months	.54 (.49)				490
Anxiety 36 months	.92 (.26)				490

[1] The No diagnosis group contains all participants who were assessed, but did not get any diagnosis or sub-threshold diagnosis.

[2] The ASD group contains the participants who were assessed and got a diagnosis of autistic disorder, Asperger syndrome, profound disability with autism, PDD NOS, sub-threshold autistic disorder, sub-threshold Asperger syndrome or sub-threshold PDD NOS.

[3] The Other diagnosis group contains the participants who were assessed and got a diagnosis of Language disorder, Mental retardation, Childhood disintegrative disorder, Other psychiatric or neurodevelopmental disorder, sub-threshold Language disorder, sub-threshold Other psychiatric or neurodevelopmental, Rett syndrome.

Table 7 shows the prevalence of sleep problems among the preschool children in the sample. The included groups differed in frequency of sleep problems, both at 18 and 36 months of age. When the children were 18 months, 10.7% of the mothers of children within the autism spectrum, reported that their child was having sleep problems. The prevalence increased to 16% when measured at 36 months. This is a contrast to the No Diagnosis group where we observed a prevalence of 3.6% of sleep problems at 18 months-, and a decrease of sleep problems to 1.54% at 36 months.

Table 7 Predictors by Sleep Problems at 18 and 36 months

	Sleep problem (18)	Sleep problem (36)
	Frequency	Frequency
ASD	8 (10.66%)	12 (16%)
No Diagnosis	7 (3.6%)	3 (1.54%)
Other Diagnosis	11 (4.97%)	17 (7.69%)
Total	26	32

Furthermore, 11% of the children with ASD qualified for a diagnosis of insomnia characterized by nocturnal awakenings, 12% qualified for a diagnosis of insomnia characterized by sleep onset delay, and 22.7 % qualified for a diagnose of parasomnia characterized by night terror (See Table 8). In total 42.6% of the children with ASD qualified for any of the insomnia diagnoses.

Table 8 Predictors by Insomnia

	Insomnia (3-5 years of age)			Any	Total
	Nocturnal awakenings	Sleep onset delay	Night terror	insomnia	
	Frequency	Frequency	Frequency	Frequency	
ASD	8 (11%)	9 (12%)	17 (22.7%)	32 (42.6%)	75
No Diagnosis	14 (7.2%)	24 (12.3%)	43 (22.2%)	63 (32.5%)	194
Other Diagnosis	24 (10,8%)	28 (12.6%)	45 (20.4%)	82 (37.1%)	221
Total	46	61	105	177	490

In addition, we conducted a regression analysis of whether sleep problems at 18 and 36 months predicted any insomnia at 3-5 years of age (See Table 9). The results indicated that sleep problems at 18 and 36 months both significantly predicted insomnia characterized by nocturnal awakenings. However, sleep problems at 18 and 36 months did not predict insomnia characterized by sleep onset delay.

Table 9 Predicting Insomina characterized by Nocturnal awakenings and Sleep onset delay

	Insomnia (3-5 years of age)	
	Nocturnal awakenings	Sleep onset delay
Sleep problems (18)	4.68* (CI 1.76-12.44)	.525 (CI .110-2.498)
Sleep problems (36)	2.95* (CI 1.136-7.68)	1.21 (CI .383-3.862)

*$p < .002$ and $p < .026$

3.2 Logistic regression analyses

To test the hypotheses binary logistic regression analysis was used according to the principles of mediation analysis.

3.2.1 Hypothesis 1: ASD and anxiety

The analysis at step 1 assessed whether the predictor ASD had an impact on the sub-types of anxiety. Table 10 indicates that the diagnosis of ASD significantly predicted generalized anxiety disorder (GAD) in preschool children ($p < .035$). Based on the results from the logistic regression analysis, the expected odds ratio for GAD between ASD and non-ASD preschool children was 2.33. This implies that the odds is 2 times higher for mothers who had children with ASD to report symptoms of generalized anxiety than those who did not have ASD. ASD was not found to be a predictor of the remaining sub-types of anxiety disorders. However, the prevalence rates were high.

3.2.2 Hypthesis 2: ASD and sleep problems

The analysis at step 2 assessed whether the predictor ASD had an impact on sleep problems at 18 and 36 months. The predictor ASD was significant for sleep problems at 18 months, $p < .031$. Based on the results from the logistic regression analysis, the expected odds ratio for sleep problems between ASD and non-ASD preschool children was 3.19. This indicates that the odds is 3 times higher for participants who had children with ASD to report sleep problems at 18 months than those who did not have ASD.

Table 10 Logistic Regression Likelihood of Generalized Anxiety[4]

		p	Odds ratio	95.0% C.I. for Odds Ratio	
				Lower	Upper
Predicting Generalized Anxiety (3-5 y)					
Step 1	ASD	.035	2.33	1.062	5.124
	Constant	.000	.09		
Predicting Sleep problems 18 months					
Step 2a	ASD	.031	3.190	1.114	9.134
	Constant	.000	.037		
Predicting Sleep problems at 36 months					
Step 2b	ASD	.000	12.127	3.316	44.355
	Constant	.000	.016		
Predicting Generalized Anxiety (3-5 y)					
Step 3a	Sleep problems (18)	.019	2.983	1.196	7.442
	Constant	.123	.123		
Step 3b	Sleep problems (36)	.005	3.266	1.430	7.458
	Constant	.000	.120		
Predicting Generalized Anxiety (3-5 y)					
Step 4a	ASD	.061	2.144	.966	4.759
	Sleep problems (18)	.035	2.707	1.071	6.843
	Constant	.000	.085		
Step 4b	ASD	.110	1.943	.860	4.390
	Sleep problems (36)	.021	2.733	1.168	6.398
	Constant	.000	.088		

The predictor ASD was also significant for sleep problems at 36 months, $p < .000$. The expected odds ratio for sleep problems at 36 months between ASD and non-ASD preschool children was 12.13 (95% CI, .3.31 to 44.35). This indicates that the odds was 12 times higher for participants who had children with ASD to report sleep problems at 36 months than those who did not have ASD.

The analysis at step 3 examined whether the predictor sleep problems at 18 months and 36 months had an impact on the sub-types of anxiety disorders. In examining generalized anxiety (see Table 10), the predictor sleep problem (18 months) was significant, $p < .019$. Based on the results from the logistic regression analysis, the expected odds ratio for GAD between preschool children with sleep problems or without sleep problems was 2.98. The odds was nearly 3 times higher for mothers who had children with sleep problems at 18 months to

[4] Table 10 shows the process of mediation analyses. At step 1, the relationship between the independent variable (ASD) and the dependent variable (Generalized anxiety) was examined. At step 2a and 2b, the relationship between the independent variable (ASD) and the mediator (sleep problems at 18 and 36 months) was examined. At step 3a and 3b, the relationship between the mediator (sleep problems at 18 and 36 months) and the dependent variable (Generalized anxiety) was examined. At Step 4a and 4 b), the relationship between the independent variable (ASD) and the dependent variable (Generalized anxiety) was examined once again, now controlled for the mediator.

report generalized anxiety than those who did not have sleep problems at 18 months. Furthermore, the predictor sleep problems (36 months), was significant, $p < .005$. Based on the results from the logistic regression analysis, the expected odds ratio for GAD between preschool children with sleep problems or without sleep problems was 3.26. This indicates that the odds was 3 times higher for mothers who had children with sleep problems at 36 months to report generalized anxiety than those who did not have sleep problems at 36 months.

3.2.3 Hypothesis 3: Indirect effects (mediation) of ASD on anxiety

The analysis at step 4 examined the indirect effect of sleep problems on the relationship between ASD and subtypes of anxiety. When examining generalized anxiety as the outcome variable, the predictor sleep problems (18 months) was significant, $p < .035$. Based on the results from the logistic regression analysis, the expected odds ratio for GAD between preschool children with sleep problem at 18 months and without sleep problems at 18 months was 2.70 (95% CI, 1.07 to 6.84). This implies that the odds is nearly 3 times higher for reporting generalized anxiety if the child had had sleep problems at 18 months. When adjusted for Sleep problem (18 months), the effect of ASD on Generalized Anxiety was no longer statistically significant, $p < .061$. When adjusted for sleep problems (36 months), the predictor sleep problems (36 months) was significant, $p < .021$. The expected odds ratio for GAD between preschool children with sleep problems at 36 months or without sleep problems at 36 months was 2.73 (95% CI, 1.17 to 6.39). The odds for mothers who have children with sleep problems (36 months) are over 2 times more likely to report generalized anxiety in preschool age. Other covariates, sex and anxiety at 18 and 36 months, were included in the regression analysis. The covariates, sex and anxiety (18 months), indicated no significant association with generalized anxiety. However, when adjusting for anxiety (36 months), a significant association with generalized anxiety, $p <.002$ was indicated.

Figure 4 illustrates the effect of ASD on Generalized anxiety before and after introducing the potential mediator, sleep problems. When adjusted for Sleep problem (18 months), the effect of ASD on Generalized Anxiety became no longer statistically significant, $p < .061$.

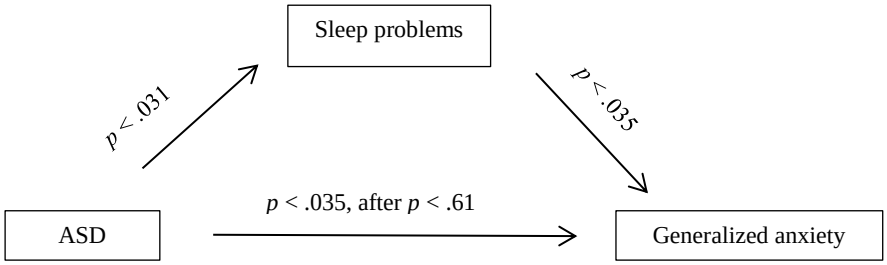

Figure 4 An illustration of the mediation process

The Sobel test was conducted to examine the magnitude of the mediation effect and it´s statistical significance (Preacher & Hayes, 2004). The test suggested mediation when a one-tailed test (t = 1.64, $p < .04$) was conducted. However, when conducting a two-tailed test the mediation effect was no longer statistically significant (t = 1.64, p < .09).

No significant association between ASD and social anxiety was found ($p < .463$) (See Table 11). However, the expected odds ratio for social anxiety was 1.4 (95% CI, .549 to 3.744).

Table 11 Logistic Regression Likelihood of Social Anxiety[5]

		p	Odds ratio	95.0% C.I. for Odds Ratio	
				Lower	Upper
Predicting Social Anxiety (3-5 y)					
Step 1	ASD	.463	1.433	.549	3.744
	Constant	.000	.072		
Predicting Sleep problem 18 months					
Step 2a	ASD	.031	3.190	1.114	9.134
	Constant	.000	.037		
Predicting Sleep problem at 36 months					
Step 2b	ASD	.000	12.127	3.316	44.355
	Constant	.000	.016		
Predicting Social Anxiety (3-5 y)					
Step 3a	Sleep problem (18)	.010	3.567	1.347	9.443
	Constant	.000	.084		
Step 3b	Sleep problem (36)	.415	1.579	.526	4.739
	Constant	.000	.090		
Predicting Social Anxiety (3-5 y)					
Step 4a	ASD	.645	1.259	.473	3.352
	Sleep problem (18)	.013	3.503	1.307	9.391
	Constant	.000	.067		
Step 4b	ASD	.548	1.352	.506	3.609
	Sleep problem (36)	.530	1.434	.466	4.416
	Constant	.000	.071		

[5] Table 11 shows the process of mediation analyses. At step 1, the relationship between the independent variable (ASD) and the dependent variable (Social anxiety) was examined. At step 2a and 2b, the relationship between the independent variable (ASD) and the mediator (sleep problems at 18 and 36 months) was examined. At step 3a and 3b, the relationship between the mediator (sleep problems at 18 and 36 months) and the dependent variable (Social anxiety) was examined. At Step 4a and 4 b), the relationship between the independent variable (ASD) and the dependent variable (Social anxiety) was examined once again, now controlled for the mediator.

No significant relationship between ASD and specific anxiety was found ($p < .062$) (See Table 12). However, the expected odds ratio for specific anxiety was 1.7 (95% CI, .972 to 3.027).

Table 12 Logistic Regression predicting likelihood of specific anxiety[6]

		p	Odds ratio	95.0% C.I. for Odds Ratio	
				Lower	Upper
Predicting Specific Anxiety (3-5 y)					
Step 1	ASD	.062	1.716	.972	3.027
	Constant	.000	.347		
Predicting Sleep problem 18 months					
Step 2a	ASD	.031	3.190	1.114	9.134
	Constant	.000	.037		
Predicting Sleep problem at 36 months					
Step 2b	ASD	.000	12.127	3.316	44.355
	Constant	.000	.016		
Predicting Specific Anxiety (3-5 y)					
Step 3a	Sleep problem (18)	.059	2.156	.972	4.783
	Constant	.000	.398		
Step 3b	Sleep problem (36)	.153	1.708	.820	3.558
	Constant	.000	.401		
Predicting Specific Anxiety (3-5 y)					
Step 4a	ASD	.094	1.633	.920	2.896
	Sleep problem (18)	.089	.089	.899	4.493
	Constant	.000	.337		
Step 4b	ASD	.106	1.614	.904	2.884
	Sleep problem (36)	.286	1.505	.710	3.192
	Constant	.000	.345		

[6] Table 12 shows the process of mediation analyses. At step 1, the relationship between the independent variable (ASD) and the dependent variable (Specific anxiety) was examined. At step 2a and 2b, the relationship between the independent variable (ASD) and the mediator (sleep problems at 18 and 36 months) was examined. At step 3a and 3b, the relationship between the mediator (sleep problems at 18 and 36 months) and the dependent variable (Specific anxiety) was examined. At Step 4a and 4 b), the relationship between the independent variable (ASD) and the dependent variable (Specific anxiety) was examined once again, now controlled for the mediator.

No relationship between ASD and separation anxiety was found ($p < .186$) (See Table 13). The expected odds ratio for separation anxiety was 1.5 (95% CI, .822 to 2.746).

Table 13 Logistic Regression Likelihood of Separation Anxiety[7]

		p	Odds ratio	95.0% C.I. for Odds Ratio	
				Lower	Upper
Predicting Separation Anxiety (3-5 y)					
Step 1	ASD	.186	1.502	.822	2.746
	Constant	.000	.276		
Predicting Sleep problem 18 months					
Step 2 a	ASD	.031	3.190	1.114	9.134
	Constant	.000	.037		
Predicting Sleep problem at 36 months					
Step 2 b	ASD	.000	12.127	3.316	44.355
	Constant	.000	.016		
Predicting Separation Anxiety (3-5 y)					
Step 3a	Sleep problem (18)	.430	1.413	.598	3.339
	Constant	.000	.314		
Step 3b	Sleep problem (36)	.601	1.238	.556	2.755
	Constant	.000	.316		
Predicting Separation Anxiety (3-5 y)					
Step 4a	ASD	.213	1.471	.801	2.699
	Sleep problem (18)	.514	1.335	.561	3.175
	Constant	.000	.273		
Step 4b	ASD	.106	1.614	.904	2.884
	Sleep problem (36)	.286	1.505	.710	3.192
	Constant	.000	.345		

[7] Table 13 shows logistic regression likelihood of separation anxiety. At step 1, the relationship between the independent variable (ASD) and the dependent variable (Separation anxiety) was examined. At step 2a and 2b, the relationship between the independent variable (ASD) and the mediator (sleep problems at 18 and 36 months) was examined. At step 3a and 3b, the relationship between the mediator (sleep problems at 18 and 36 months) and the dependent variable (Separation anxiety) was examined. At Step 4a and 4 b), the relationship between the independent variable (ASD) and the dependent variable (Separation anxiety) was examined once again, now controlled for the mediator.

4 Discussion

4.1 Main findings

The main aim of this study, using prospective longitudinal data, was to examine the relationship between early age sleep problems and ASD among preschool children with anxiety. A significant relationship between ASD and generalized anxiety disorder (GAD) was found. In addition there was a significant association between ASD and sleep problems at 18 months of age. The association was even stronger at 36 months of age. A significant association between sleep problems at 18 months and generalized anxiety in preschool children was found, and the association remained significant after controlling for sex and anxiety at 18 months. The effect of ASD on generalized anxiety was reduced when we adjusted for sleep problems at 18 months. This suggests that the relationship between ASD and generalized anxiety may be at least partly mediated by sleep problems at 18 months. No relationship was found between ASD and the remaining subtypes of anxiety, separation anxiety, specific anxiety and social anxiety, in this sample.

4.1.1 Associations between ASD and anxiety in preschool children

Previous studies have concluded that anxiety is common in individuals with ASD. However, few studies have examined the association between subtypes of anxiety in preschool children. The findings of the current study both support and contradict previous studies. The current study revealed a significant relationship between ASD and generalized anxiety. It supports the findings of Kim et al. (2000) and Sukhodolsky et al. (2008) who found a significant association between ASD and generalized anxiety in children and adolescents with ASD (Kim et al., 2000; Sukhodolsky et al., 2008). As mentioned earlier, generalized anxiety (GAD) includes multiple worries about a variety of life circumstances (Pine & Klein, 2008). The significant relationship between ASD and generalized anxiety may support the argument of Sukhodolsky et al., (2008) that "insistence of sameness" reflects anxiety. Changes in routines and interruption of stereotyped behaviors may increase generalized anxiety symptoms, i.e. muscle tension, and further emotionally upset the children with ASD. In addition, it is also reasonable to think that, because of the social-emotional deficits observed in ASD, children

with ASDs may experience a great deal of stress from an early age. They may be at risk for developing comorbid psychopathology because of a limited ability to modulate responses to stress (Pearson, Loveland, & Lachar, 2006). Another explanation of the significant relationship between ASD and generalized anxiety may be of neurobiological character. There is evidence from human and animal studies which shows that the amygdala plays a substantial role in autism (Bachevalier & Loveland, 2006). The amygdala is an early-developing medial temporal lobe brain structure that is involved in detection and evaluation of experiences with emotional significance (Bachevalier & Loveland, 2006). It is developmentally linked in a circuit with the orbitofrontal cortex, a region that has been found to be involved in self-regulation of emotion and behavior in response to a changing environment (Bachevalier & Loveland, 2006). Bachevalier and Loveland (2006) argue that developmental impairment of this circuit may explain the special difficulties in self-regulation experienced by children with autism (Bachevalier & Loveland, 2006). The underlying neurobiological differences associated with autism may also make children more vulnerable to developing a generalized anxiety disorder (Pearson et al., 2006). Another possible explanation is the hypothesis in the current study that sleep problems at an early age work as triggers for developing generalized anxiety disorders in preschool children with ASD. This will be discussed in section 4.1.3.

No significant relationship was found between ASD and separation anxiety, ASD and specific anxiety and ASD and social anxiety. These findings contradict the findings of Sukhodolsky et al. (2008) who found a significant relationship between ASD and separation anxiety, and ASD and specific phobia. However, it is important to keep in mind that no previous studies have used validated diagnostic interviews for measuring subtypes of anxiety in preschool children with ASD. Hence, the current results are unique because of the application of the Preschool Age Psychiatric Assessment Interview (PAPA) (Egger & Angold, 2004). Several of the previous studies have used questionnaires and samples of subjects with ASD identified from clinical treatment studies. Because of this, it is possible that the higher rates of anxiety problems in these studies are due to ascertainment bias, so called Berkson´s bias (Last, 2007).

> ‘‘*Berkson´s bias is a form of selection bias that causes hospital cases in a case control study to be systematically different from one another because of the combination of exposure to risk and occurrence of disease increases the likelihood of being admitted to*

the hospital. This produces a systematically higher exposure rate among hospital patients, so it distorts the odds ratio" (Last, 2007).

Nevertheless, our findings support the findings of Weisbrot et al. (2005) that there is no significant relationship between ASD and separation anxiety, social anxiety and specific anxiety in preschool children. In addition, our findings support the findings of Sukhodolsky et al. (2008) in that there is no significant association between ASD and social anxiety. As mentioned earlier, the diagnostic distinction between severe social anxiety disorder and mild pervasive development disorder can be problematic. Assessment of social anxiety in children with ASD is complicated because of limited verbal skills, cognitive deficits, and lack of insight into one´s own difficulties and emotional states (MacNeil et al., 2009). However, ASD is a heterogeneous group where individuals differ in degree of impairments in reciprocal social interaction and impairments in communication skills (APA, 2000). It may be difficult to measure whether the lack of interest in social interaction are due to the child´s lack of social competence, anxiety and uncomfortableness in social settings, or merely is a need for one´s own space.

4.1.2 Associations between ASD and sleep problems

The current results indicate a significant relationship between having a sleep problem at 18 months and an ASD diagnosis at 3-5 years. The association was even stronger at 36 months of age. This is the first longitudinal study, conducted in Norway, of early age sleep problems in children with ASD using prospectively collected data. The current results support the findings of Avon Longitudinal Study of Parents and Children (ALSPAC) conducted by Humphreys et al (2014). The significant relationship found between sleep problems and ASD might imply that having a neurodevelopmental disorder does not only result in core ASD symptoms, but also impairs regulation of sleep. This finding adds evidence to the assumption of Sikora et al. (2012), who emphasized that having a neurodevelopmental disorder might not only result in core ASD symptoms, but also impaired behavior and regulation of sleep (Sikora et al., 2012).

In addition, the current study gives support to the evidence of early age sleep disturbances in ASD (Humphreys et al., 2014), but does not indicate what kind of sleep problems which are present at 18 months. However, it was found that 11 % of the preschool children with ASD had nocturnal awakenings, measured with PAPA. In addition, the results indicated that sleep problems at 18 and 36 months both significantly predicted insomnia characterized by

nocturnal awakenings at 3-5 years of age. However, sleep problems at 18 and 36 months did not predict insomnia characterized by sleep onset delay. Overall, the current study adds support to previous studies that insomnia is a substantial problem for preschool children with ASD, with a prevalence of 42.6%.

The results support previous findings of Krakowiak et al. (2008) and Richdale et al. (2009) that insomnia (in particular sleep onset, settling, and night-waking problems) issues are a hallmark of sleep problems for preschool children with ASD (Krakowiak et al., 2008; Richdale & Schreck, 2009). Although the current results indicate that sleep problems are associated with ASD, the reasons for this are yet unclear. As previously mentioned, abnormalities in neurobiological networks regulating sleep is found in autism (Johnson et al., 2009). The clinical review of Richdale and Schreck (2009) concludes that there is preliminary evidence which suggests that an abnormality in melatonin production and circadian timing might be causative in both insomnia and circadian sleep disturbances in ASD. In the systematical review and meta-analysis of Rossignol and Frye (2011), it is argued that melatonin administration in ASD is associated with improved sleep parameters, better daytime behavior, and minimal side effects. Humphreys et al., (2014) also argue for further consideration of using melatonin to reduce sleep problems in children with ASD. This may be difficult to implement because of the challenges of early detection of ASD in infants.

Anxiety at 18 and 36 months of age were controlled for and the implication of these covariates will be discussed in the following section.

4.1.3 Associations between ASD and generalized anxiety may be accounted for by the mediating role of sleep problems

The current study used the causal steps approach of mediation analysis. The significance of the relationship between ASD and generalized anxiety were tested both before and after controlling for the mediator sleep problems. This was conducted in order to examine the validity of a theory specifying mediation (Rucker et al., 2011). The significant relationship between ASD and generalized anxiety was reduced when sleep problems at 18 months were adjusted for. May sleep problems at 18 months of age have an important role in the developmental pathway of generalized anxiety disorder in preschool children with ASD? This finding may imply that the association between ASD and generalized anxiety can be at least partially accounted for by the mediating effect of sleep problems at 18 months. Thus, this may

indicate that children with ASD who sleeps well at 18 months are less a risk for developing a generalized anxiety disorder in preschool age. Furthermore, when we controlled for anxiety at 18 months of age the significant mediating role of sleep problems was still present. Hence, it is reasonable to think that there may be something in the abnormalities in neurobiological networks regulating sleep, which contribute to sleep disturbances in ASD (Johnson et al. 2009). These sleep disturbances seem to have a triggering/ mediating effect on the development of generalized anxiety in preschool children with ASD, but in what way this triggering effect works remains to be investigated. Thus, ASD may work as a vulnerability factor for developing sleep problems and sleep problems may constitute a risk factor for developing generalized anxiety in infants with ASD.

Previous research has shown that anxiety is common in children with ASD (White et al., 2009). In examining subtypes of anxiety disorders, results of the current study merely found a significant association between generalized anxiety and ASD. Disturbance of sleep in preschool children with ASD may lead to increased emotional disturbance, perhaps through biologically or cognitively mediated mechanisms. Furthermore, early age sleep problems may simply be a marker for developing psychopathology in preschool children with ASD, including generalized anxiety.

4.1.4 Limitations

The current study used a population-based design, with a prospective data collection, and a method to identify ASD cases, unique in the research field of autism spectrum disorders. In contrast to most clinical studies, both children with mild and severe ASD symptoms and the sub-threshold diagnoses were included in analyses. The diagnoses were determined when the children were 3 years or older, an age when ASD diagnoses are reported to be fairly stable (Stenberg et al., 2014; Lord, C. et al 2006). The use of a validated diagnostic interview, PAPA, in examining subtypes of anxiety and sleep problems in preschool children with ASD exceeds previous research in this field. No research has previously been conducted on the potential mediating role of sleep problems on the relationship between ASD and anxiety.

However, the results should be viewed in the light of some limitations. First, the measure of sleep problems at 18- and 36 months of age may not be very differentiated and accurate. The threshold for answering positively to the question of whether the child has sleep problems can be argued in two ways. The threshold may be relatively high or low for mothers to define

whether their child´s disturbances in sleep-wake rhythm are a problem or not. Thus, mothers may be uncertain of what is normal and what is not normal. Secondly, another limitation is the lack of multiple informants in the current study. However, the interviewer was trained to note if the answer corresponded to fulfillment of a symptom. Another limitation is that the sample size of ASD was relatively low. Hence, the findings may not be generalizable to other samples of autism spectrum disorders. Lastly, the principles of mediation analysis claim that an independent variable must precede the mediator (Baron & Kenny, 1986). With this in mind and thus, ASD is a biologically based neurodevelopmental disorder (Stoltenberg et al., 2010), it was assumed that the children who had sleep problems (mediator) at 18 months and received a diagnosis of ASD (independent variable) in the ABC-clinic, also had the same biologically characteristics of ASD by 18 months.

4.1.5 Potential clinical implications and future directions

It is reasonable to think that problems with generalized anxiety in children with ASD may cause additional social and developmental impairment. Given that ASD and sleep problems independently predict generalized anxiety, prevention and treatment plans for generalized anxiety may consistently focus on improving sleep in children with ASD at 18 months of age. This may be problematic because of the challenges of early detection of ASD. However, the current findings suggest that it may be important to routinely assess sleep disturbances in children at 18 months. Further examinations on linking the neurotransmitter abnormalities, found in ASD, to severity of sleep disturbances are needed. The current study adds a new insight for the protective implication good sleep hygiene may have on the pathway of developing generalized anxiety in preschool children with ASD.

5 Conclusion

The current results suggest that having sleep problems at 18 months of age may be an important consideration in understanding development of generalized anxiety disorder in children with ASD. Further research is needed to better characterize the processes by which sleep problems may affect the development of generalized anxiety among children with ASD. Given the potential for early intervention to alter the developmental course of generalized anxiety in children with ASD, the current results recommend health services to be attentive to sleep disturbances in children who have received a diagnosis of ASD at 18 months of age.

Overall, the aim of the current study was to examine the relationship between early age sleep problems and ASD among preschool children with anxiety. The current findings suggest that the significant relationship between ASD and generalized anxiety can at least partially be accounted for by the mediating role of sleep problems in children with ASD.

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Appendix

Excerpts of the MoBa Questionnaire at 18 months:

http://www.fhi.no/dokumenter/2640dd4bcc.pdf

Sleep problems

Health problem	No	Yes, has now	Yes, had previously	If yes, has child been referred for specialist examination? No	Yes
4. Delayed motor development (e.g. sits/walks late)	☐	☐	☐	☐	☐
5. Too little weight gain	☐	☐	☐	☐	☐
6. Too much weight gain	☐	☐	☐	☐	☐
7. Abnormal head circumference	☐	☐	☐	☐	☐
8. Heart defect	☐	☐	☐	☐	☐
9. Testicles not descended into scrotum	☐	☐	☐	☐	☐
10. Asthma	☐	☐	☐	☐	☐
11. Atopic eczema (childhood eczema)	☐	☐	☐	☐	☐
12. Urticaria (hives)	☐	☐	☐	☐	☐
13. Food allergy/intolerance	☐	☐	☐	☐	☐
14. Late or abnormal speech development	☐	☐	☐	☐	☐
15. Sleep problems	☐	☐	☐	☐	☐
16. Behavioural problems	☐	☐	☐	☐	☐
17. Social problems	☐	☐	☐	☐	☐
18. (Other) malformations: _____	☐	☐	☐	☐	☐
19. Other: _____	☐	☐	☐	☐	☐

Anxiety

37. To what extent are the following statements true of your child's behaviour during the last two months? *(Enter a cross in a box for each item.)*

	Not true	Somewhat or sometimes true	Very true or often true
1. Can't concentrate, can't pay attention for long	☐	☐	☐
2. Quickly shifts from one activity to another	☐	☐	☐
3. Can't sit still, restless or hyperactive	☐	☐	☐
4. Gets into everything	☐	☐	☐

(cont.)

+	Not true	Somewhat or sometimes true	+	Very true or often true
5. Is mostly happy and contented	☐	☐		☐
6. Clings to adults or too dependent	☐	☐		☐
7. Gets too upset when separated from parents	☐	☐		☐
8. Gets into many fights	☐	☐		☐
9. Hits others	☐	☐		☐
10. Is defiant	☐	☐		☐
11. Doesn't seem to feel guilty after misbehaving	☐	☐		☐
12. Punishment doesn't change his/her behaviour	☐	☐		☐
13. Doesn't eat well	☐	☐		☐
14. Likes almost every kind of food	☐	☐		☐
15. Resists going to bed at night	☐	☐		☐
16. Doesn't want to sleep alone	☐	☐		☐
17. Afraid to try new things	☐	☐		☐
18. Disturbed by any change in routine	☐	☐		☐
19. Too fearful or anxious	☐	☐		☐

Excerpts of the MoBa Questionnaire at 36 months:

http://www.fhi.no/dokumenter/c43798ed4a.pdf

Sleep problem

The following questions concern any illnesses or health problems your child has had. We will first ask you about longer-term problems and then about illnesses and problems of a more acute nature.

3. Has your child suffered any long-term illness or health problems since the age of 18 months?

Health problem	No	Yes, has now	Yes, had previously	If so, has child been referred to a specialist: No	Yes
1. Impaired hearing	☐	☐	☐	☐	☐
2. Impaired vision	☐	☐	☐	☐	☐
3. Delayed motor development (e.g. sits/walks late)	☐	☐	☐	☐	☐
4. Cerebral palsy	☐	☐	☐	☐	☐
5. Joint problems	☐	☐	☐	☐	☐
6. Diabetes	☐	☐	☐	☐	☐
7. Gained too little weight	☐	☐	☐	☐	☐
8. Gained too much weight	☐	☐	☐	☐	☐
9. Heart defect	☐	☐	☐	☐	☐
10. Testicles not descended into scrotum	☐	☐	☐	☐	☐
11. Asthma	☐	☐	☐	☐	☐
12. Allergy affecting eyes or nose, e.g. hay fever	☐	☐	☐	☐	☐
13. Atopic eczema (childhood eczema)	☐	☐	☐	☐	☐
14. Other type of eczema	☐	☐	☐	☐	☐
15. Frequent diarrhoea	☐	☐	☐	☐	☐
16. Frequent stomach pains	☐	☐	☐	☐	☐
17. Food allergy/intolerance	☐	☐	☐	☐	☐
18. Other gastrointestinal problems	☐	☐	☐	☐	☐
19. Late or abnormal speech development	☐	☐	☐	☐	☐
20. Sleep problems	☐	☐	☐	☐	☐
21. Trouble relating to others	☐	☐	☐	☐	☐
22. Hyperactivity	☐	☐	☐	☐	☐
23. Autistic traits	☐	☐	☐	☐	☐
24. Other behavioural problems	☐	☐	☐	☐	☐
25. Other long-term illness/condition	☐	☐	☐	☐	☐

Specify _____

27. To what extent do the following statements apply to your child's behaviour during the last two months? *(Enter a cross in a box for each item.)*

	Very typical	Quite typical	Neither/ nor	Not so typical	Not at all typical
1. Your child cries easily	☐	☐	☐	☐	☐
2. Your child is always on the go	☐	☐	☐	☐	☐
3. Your child prefers playing with others rather than alone	☐	☐	☐	☐	☐
4. Your child is off and running as soon as he/she wakes up in the morning	☐	☐	☐	☐	☐
5. Your child is very sociable	☐	☐	☐	☐	☐
6. Your child takes a long time to warm up to strangers	☐	☐	☐	☐	☐
7. Your child gets upset or sad easily	☐	☐	☐	☐	☐
8. Your child prefers quiet, inactive games to more active ones	☐	☐	☐	☐	☐
9. Your child likes to be with people	☐	☐	☐	☐	☐
10. Your child reacts intensely when upset	☐	☐	☐	☐	☐
11. Your child is very friendly with strangers	☐	☐	☐	☐	☐
12. Your child finds other people more fun than anything else	☐	☐	☐	☐	☐
13. Your child complains that certain garments are too tight	☐	☐	☐	☐	☐
14. Your child is distressed by having his/her face or hair washed	☐	☐	☐	☐	☐

28. The following list contains statements describing children's behaviour and manner from the age of 2-3. Some of these features are temporary while others continue for a longer period of time. To what extent are the following statements true of your child's behaviour during the last two months? *(Enter a cross in a box for each item.)*

	Not true	Somewhat or sometimes true	Very true or often true
1. Afraid to try new things	☐	☐	☐
2. Can't concentrate, can't pay attention for long	☐	☐	☐
3. Can't sit still, restless or hyperactive	☐	☐	☐
4. Can't stand waiting, wants everything now	☐	☐	☐
5. Clings to adults or too dependent	☐	☐	☐
6. Constipated, doesn't move bowels	☐	☐	☐
7. Defiant	☐	☐	☐
8. Demands must be met immediately	☐	☐	☐
9. Disturbed by any change in routine	☐	☐	☐
10. Doesn't want to sleep alone	☐	☐	☐
11. Doesn't eat well	☐	☐	☐
12. Doesn't seem to feel guilty after misbehaving	☐	☐	☐
13. Eats or drinks things that are not food (don't include sweets)	☐	☐	☐
14. Gets in many fights	☐	☐	☐
15. Gets into everything	☐	☐	☐
16. Gets too upset when separated from parents	☐	☐	☐
17. Hits others	☐	☐	☐
18. Poorly coordinated or clumsy	☐	☐	☐
19. Punishment doesn't change his/her behaviour	☐	☐	☐
20. Quickly shifts from one activity to another	☐	☐	☐
21. Resists going to bed at night	☐	☐	☐
22. Stomach aches or cramps (without medical cause)	☐	☐	☐
23. Sudden changes in moods or feelings	☐	☐	☐
24. Too fearful or anxious	☐	☐	☐
25. Vomiting, throwing up (without medical cause)	☐	☐	☐
26. Doesn't seem to be happy eating food (don't include sweets)	☐	☐	☐

Computer generated diagnoses of primary insomnia and parasomnia used in the current study:

Insomnia characterized by nocturnal awakenings:

if (Leaves bed=2 AND Night awakenings=1) Insomnia=Perturbation.

if (Leaves bed=2 AND (Night awakenings>1 AND Night awakenings<5)) Insomnia=Disturbance.

if (Leaves bed=2 AND Night awakenings>=5) Insomnia=Disorder.

Insomnia characterized by sleep onset delay:

if (Time to fall asleep>20 OR Use of sleep medication=1) Insomnia=Sleep onset delay.

Parasomina characterized by sleep terror:

if (Night terror=2) Parasomnia=Night terror